REMARKS

Claims 1-44 are pending. Claims 1-31 and 39-41 have been withdrawn from consideration. Claims 32-38 and 42-44 are rejected. Claim 38 has been amended. Claims 1-44 remain in the case.

As requested by the examiner, applicants by separate letter propose a drawing change to label Figure 3 as two figures, Figure 3A and 3B. Corresponding changes to the specification have been made. The examiner indicates that the PTO file is missing Figure 7, and a copy is provided herewith. Figure 7 shows the carbohydrate structures for known cancer mucins that are described in the specification.

Claims 32-38 and 42-44 are rejected under Section 101 and under the first paragraph of Section 112. The examiner urges that the specification fails to provide a specific asserted utility for the claimed glycopeptide combinatorial library as presently claimed. In this regard, the examiner asserts that "screening is not a specific utility." He further asserts that "a library is nothing more than a collection of mixtures of known or existing products that cannot be categorized as new and has to be screened to discover a new compound or composition contained therein." This statement is, on its very face, contradictory. That is, the examiner on the one hand alleges that the library contains only "known or existing products that cannot be categorized as new," and in the next breath urges that the library has to be screened "to discover a new compound or composition contained therein"! Indeed, a combinatorially generated glycopeptide library according to the present invention will contain a large number of new compounds, many of which will have useful biological activity.

The examiner cites MPEP §2107, although his statements relating to its guidance are less than clear. MPEP §2107 quite clearly states that inventions that are useful in a research setting may indeed have "a clear, specific and unquestionable utility," citing such research tools as screening assays and nucleotide sequencing techniques. It is submitted that a combinatorially-generated glycopeptide library is just such a tool, and thus patentable under Section 101.

The examiner notes that "a patent application is not a hunting license rather, a reward for successful accomplishments of a search." A skilled artisan need not go

"hunting" to find a combinatorially-generated glycopeptide according to the invention. The specification clearly places such a library in the hands of the public, where it will provide a useful tool in identifying biologically-active compounds. Moreover, the USPTO has granted other patents with claims to combinatorial libraries, including very large combinatorial libraries. For example, U.S. 5,738,996 claims a large peptide combinatorial peptide library for selecting oligomer compounds that react with an unspecified macromolecular ligand (a copy of the claims is attached) and U.S. 6,268,140 claims a combinatorial library comprising a plurality of heterologous nucleic acids capable of expressing all or part of a metabolic pathway in a cell (claim 1 is attached). As to the latter, a library having 4-base variability at 8 oligomer residue positions would contain as many as 4^8 (65,536) different sequences, while a peptide library with 20-amino acid variability at six residue positions will contain as many as 20.sup.6 (64,000,000) different species. Yet libraries of this size and larger are routinely screened for active compounds. Clearly, claims to combinatorial libraries, even very large ones that are not defined in structural detail, are useful and enabled.

The examiner appears to fear that granting a claim to such a library would grant to applicant rights in each and every useful compound contained in such a library, thus precluding others from isolating, identifying and patenting specific compounds in such a library. Applicants do not, however, claim individual compounds. Reconsideration and withdrawal of the rejection under Sections 101 and 112 is respectfully requested.

Claims 32-38 and 42-44 are further rejected under the first paragraph of Section 112, based on the recitation of screening the library for specified activities While all claims under examination are included in the rejection, it appears that only claim 38 should be rejected, since the language objected to by the examiner appears only in claim 38. More particularly, the examiner previously objected to the recitation of "antibody-like" activity in claim 38, and applicants responded by reciting "antibody" activity. The examiner now says that "antibody" activity is not supported in the as-filed specification because "the specification describes a compound that only resembles or has an antibody-like property." However, the claims do not recite that any compound in the library is an antibody, only that they may be screened for antibody activity. It is submitted that a compound that "mimics" an antibody activity is appropriately claimed as one having antibody activity.

The examiner further argues that applicants fail to describe a library that has competitive inhibitory, immunostimulatory, or antibody activity. Armed with applicants' disclosure of how to produce a combinatorial glycopeptide library, however, a skilled artisan readily could select platforms and carbohydrates to produce a library of compounds likely to contain some with the recited activities.

Claims 32-38 and 42-44 are further rejected under the first paragraph of Section 112 for allegedly failing to enable "the broadly recited combinatorially-generated library of glycopeptides [other than those which have MUC1 as the core protein]." In this regard the examiner finds the disclosure on page 5 of applicants' response of January 5, 2001, to confirm the need for "undue experimentation" in the practice of the present invention. More particularly, the examiner identifies the following remarks from applicants' last response:

> In order to design competitive inhibitors and antigens, it is important to know the sites of glycosylations, as well as the nature and size of the carbohydrates at each site. If one considers the permutations and combinations that arise from all the unique sites and the variety of carbohydrates that may exist on the tandem repeat, the number of possible arrangements becomes unimaginably large... Combinatorial and random techniques, on the other hand, result in all of the statistically possible ways in which various reactants can combine without actually identifying any of them until a screening process detects a 'hit' for further analysis and identification.

The examiner then urges that a skilled artisan

> would be faced with numerous unpredictable factors such as the components of a carbohydrate and/or peptide can be comprised in a library, the site or amino acid in the peptide that can be modified by attachment of the carbohydrate moieties singly or in combinations with other components as lipids, the means of attachment, the type of library that the carbohydrate can assume *e.g.* random or biased, the type of assays that determines either a single or all activities present in the library.

In a combinatorial approach, however, the skilled artisan need not be concerned with how or where moieties are attached. The beauty of a combinatorial process is that it generates all permutations automatically, and then an automated large-scale screening assay can be used to identify useful compounds. There is widespread interest in using combinatorial libraries of random-sequence oligonucleotides, polypeptides, or synthetic oligomers to search for biologically active compounds (Kramer; Houghten, 1992, 1991; Ohlmayer; Dooley, 1993a-1993b; Eichler; Pinilla, 1993, 1992; Ecker; and Barbas).

Ligands discovered by screening libraries of this type may be useful in mimicking or blocking natural ligands, or interfering with the naturally occurring interactions of a biological target. Even very large numbers of compounds can be screened easily, to provide a manageable subset of useful compounds, and the skilled artisan can then study these useful compounds to elucidate their structure. The experimentation involved is not "undue" and combinatorial approaches have been used with other types of compounds. Indeed, combinatorial chemistry has gained widespread appeal in recent years.

The examiner finds claim 38 to be "confusing" and it has been amended to address the examiner's stated concerns.

Based on the foregoing, reconsideration and withdrawal of all rejections under the first paragraph of Section 112 is respectfully requested.

Claims 32-38 and 42-44 also are rejected under the second paragraph of Section 112, the examiner arguing that "the description of a library based on the method by which it is made fails to identify the structural components present in the library, *i.e.*, it fails to fingerprint the library." However, there is no other way to claim a combinatorial library. A combinatorial library, by definition, contains compounds the identity of which are unknown at the time the library is generated. To require applicants to claim the library structurally are is an impossible task. Reconsideration and withdrawal of the rejection under the second paragraph of Section 112 is respectfully requested.

Claims 32, 34-38, 42, and 43 are rejected under Section 102(e), or in the alternative under Section 103(a), based on Rao *et al.* (U.S. 5,795,958). In response to applicants' remarks of January 5th, the examiner replies that "whether the library of Rao is produced by sequential coupling of individual amino acids as opposed to the instant random reaction (which Rao also discloses) and might be a long, tedious process however, the same product *i.e.*, combinatorial library of glycopeptides is obtained by Rao as that instantly claimed." However, Rao describes collections of glycopeptides, each of which is individually synthesized using a multicolumn automated peptide synthesizer by sequentially coupling individual amino acids including pre-fucosylated serine, and subsequently combined to form a relatively small collection or library. Rao does not disclose a combinatorially-generated library of randomly glycosylated structures, and thus the so-called "library" is not "the

same product" It would not be possible to individually synthesize all glycopeptides that would be contained in a combinatorially-generated library as presently claimed – the procuess would not merely be "long" and "tedious." Rao cannot possibly be alleged to disclose libraries that would have the size and diversity of the libraries claimed by applicants, and thus cannot reasonably be said to disclose a product that is the same or similar to applicant's claimed library.

Claims 32 and 34-38 are rejected under Section 102(b) or Section 103(a) based on Vetter (WO 95/18971). Vetter *et al.* describes solid-phase methods of attaching carbohydrates (N-linked), through a linker arm, to solid supports that have no structural definition, and serve solely as an anchor, having no part in the activity of the molecule. The solid support is typically a polymer. A single compound is produced in each reaction vessel, using a solid support. As in Rao, the library is limited, and not the same as the combinatorially library presently claimed.

Claims 32-37 are rejected under Section 102(b) based on Frische *et al.* (abstract *J. Pept. Sci.*). Like Rao and Vetter, Frische *et al.* describes the synthesis of a series of peptides and glycopeptides based on the sequence of mouse hemoglobin, through solid phase techniques. Preglycosylated serine and threonine are used. Each glycopeptide is separately synthesized, and then combined to form a so-called "library."

In the present situation, the manner of making the claimed library precludes a "rationale" that the claimed product, applicant's library, is "the same or similar to that of the prior art." The prior art describes collections of individually-synthesized glycopeptides. Thus, in Rao *et al.*, each glycopeptide is individually synthesized using a multicolumn automated peptide synthesizer by sequentially coupling individual amino acids including pre-fucosylated serine, and subsequently combined to form a relatively small collection or library. Rao does not disclose a combinatorially-generated library of randomly glycosylated structures, and it would be humanly impossible to individually synthesize all glycopeptides that would be contained in a combinatorially-generated library as presently claimed. Rao cannot possibly be alleged to disclose libraries that would have the size and diversity of the libraries claimed by applicants, and thus cannot reasonably be said to disclose a product that is the same or similar to applicant's claimed library.

A similar situation exists with respect to Vetter (WO 95/18971) and Frische *et al.* The collection of structures produced in Vetter all carry a single carbohydrate structure with no provision for further iterative synthesis leading to more complex structures, as in the randomly glycosylated libraries according to applicants' invention. Similarly to Rao, Vetter's solid-phase synthesis does not lead to large numbers of randomly-glycosylated structures, such as are contained in the combinatorially-generated libraries according to the present invention. Frische *et al.* describes the synthesis of a series of peptides and glycopeptides based on the sequence of mouse hemoglobin, through solid phase techniques. Preglycosylated serine and threonine are used. Each glycopeptide is separately synthesized, as in Rao and Vetter, and then combined to form a so-called "library." The arguments presented above with respect to Rao and Vetter apply with equal force to Vetter, and there is no reasonable basis for an assumption on the part of the Patent Office that the product described in Vetter or Frische is the same or similar to that claimed by applicant.

As a summary of the differences between the present invention and the disclosures of Rao, Vetter and Frische, applicants have prepare a comparison table which is appended hereto. The table clearly shows why none of the cited references anticipate or render obvious applicants' claims to a combinatorially-generated glycopeptide library, which has tremendous diversity. Diversity is important for the discovery of biologically active components. Applicants' glycopeptide libraries provide the necessary diversity, by using combinatorial methods in which several and various carbohydrates are randomly placed on a given sequence of amino acids. This approach greatly enhances the probability of discovering biologically active molecules.

The present invention provides a way of identifying patterns in protein glycosylations. Such information is needed in the discovery of antigens for immunotherapy of cancers, inhibitors of bacterial adhesion to prevent infections, inhibitors of cell-cell adhesion to prevent inflammations etc. Random and combinatorial approaches provide the only way to deal with millions of statistically possible ways of placing a variety of carbohydrate structures along a protein core. This approach offers a fast and powerful route to discover therapeutics. Mucins (MUC) are epithelial cell surface glycoproteins, the core of which often is made of tandemly repeating short sequences. Most glycosylations are O-linked in nature, with serines and threonines being the most predominant amino acids.

Being very large in size and length, the glycosylations extend far out on the epithelial cell surface and become the foremost contact points for a variety of functional molecules, antibodies, immune cells and even for infections by pathogens like bacteria and viruses. Knowledge of their glycosylation patterns is, therefore, important and challenging. In order to design competitive inhibitors and antigens, it is important to know the sites of glycosylations, as well as the nature and size of the carbohydrates at each site. If one considers the permutations and combinations that arise from all the unique sites and the variety of carbohydrates that may exist on the tandem repeat, the number of possible arrangements becomes unimaginably large. The true glycosylation pattern of a mucin tandem repeat can only be discovered through a combinatorial approach, *i.e.*, by randomly glycosylating and generating a near true diversity to enhance the possibility of locating a tandem repeat that has the glycosylation pattern similar to that of a mucin. Synthesis of a library of thousands of glycopeptides by employing automated solid phase techniques, as in Rao, Vetter or Frische, would not be feasible. While the screening process of pure individual compounds is simpler, their synthesis even with automation yields vastly restricted diversity. Combinatorial and random techniques, on the other hand, result in all of the statistically possible ways in which various reactants can combine without actually identifying any of them until a screening process detects a 'hit' for further analysis and identification.

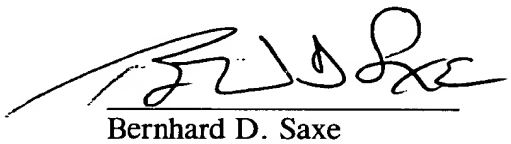
To illustrate the point, consider the core proteins of mucins, which are rich in both glycosylation sites and carbohydrate diversity. The 17 amino acid tandem repeat of human intestinal mucin MUC3 contains 12 unique sites (serines and threonines) for glycosylation. If 3 different carbohydrate structures were to chemically link to a single tandem repeat of MUC3, it is theoretically possible to create a library of over 16 million different glycopeptides with different magnitudes of glycosylation. The single most powerful benefit of having all random combinations is the ability to locate a glycopeptide with the right glycosylation pattern that is characteristic of a cancer-associated mucin. This is not achieved or suggested by Rao, Vetter or Frische.

Claims 32 and 34-38 are rejected under Section 102(a) or Section 103(a) based on Schleyer, in light of the failure of the specification to include a reference to the provisional

priority document. The specification has been so amended, obviating this ground of rejection.

In view of the foregoing amendments and remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions regarding this application, the examiner is invited to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,



September 21, 2001
Date

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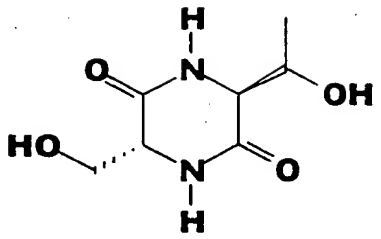
MARKED-UP VERSION OF AMENDED CLAIMS

38. (Thrice Amended) A method of identifying a biologically-active compound in a combinatorally-generated glycopeptide library, comprising:

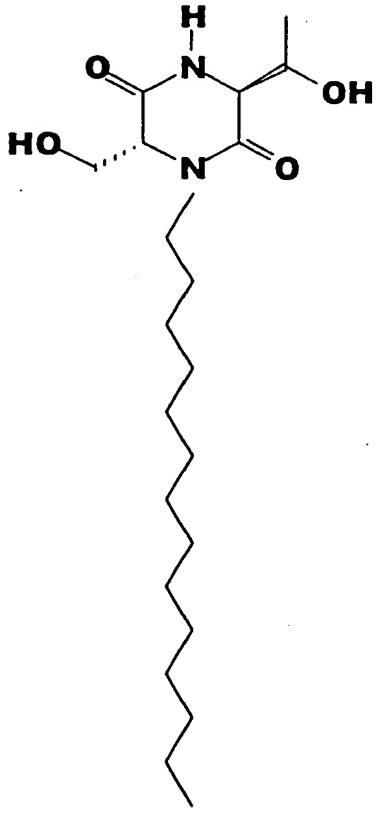
generating a library of glycosylated scaffolds according to claim 34; and

screening components of said library for a biologically-active compound that has competitive inhibitory, immunostimulatory or antibody activity.



THE SIMPLEST CYCLIC PEPTIDE

Figure 3A



A SOLUBLE VERSION OF THE ABOVE (with C_{14} lipid)

Figur 3B